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Intra-abdominal infections: the role of different classifications on the selection of the best antibiotic treatment

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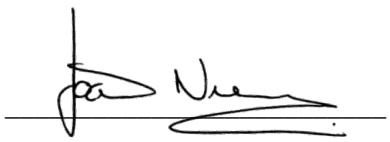

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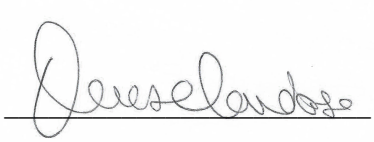

Teresa Cardoso

Date: May of 2018

"Recomeça…
Se puderes,
Sem angústia e sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro,
Dá-os em liberdade.
Enquanto não alcances
Não descanses.
De nenhum fruto queiras só metade.

E, nunca saciado,
Vai colhendo
Ilusões sucessivas no pomar
E vendo
Acordado,
O logro da aventura.
És homem, não te esqueças!
Só é tua a loucura
Onde, com lucidez, te reconheças."

Miguel Torga, ***Sísifo in Diário XIII***

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Finally, I would like to thank my parents, brother and friends for all the support, patience and love.

ABSTRACT

Introduction: Intra-abdominal infections represent one of the most frequent gastrointestinal emergencies and a serious cause of morbidity and mortality. A full classification that includes all facets of intra-abdominal infections does not exist. There are two classifications used to subdivide intra-abdominal infections: uncomplicated or complicated, founded on the extent of infection, and community-acquired, healthcare-associated or hospital-acquired, based on the place of acquisition. The adequacy of the initial empirical antibiotic therapy prescribed is an essential need. There is evidence that inadequate and/or delayed antibiotic therapy is associated with treatment failure and increased mortality.

Objectives: This study was designed to assess the impact of the different classifications of intra-abdominal infections in the selection of the best antibiotic therapy. Main objectives of the study are: to identify independent factors for intra-abdominal infection by pathogens sensitive to the antibiotic scheme recommended for community-acquired intra-abdominal infection: non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole (shorter spectrum and main outcome) or piperacillin/tazobactam; to describe the microbiological profile associated with each classification; to determine the discriminative power of each intra-abdominal infection classification to identify patients infected by a pathogen sensitive to the elected antibiotic combination; and to describe major prognostic factors associated with hospital mortality among the study population of patients with intra-abdominal infection.

Methodology: Retrospective cohort study including all adult patients discharged from the hospital with the diagnosis of intra-abdominal infection between 1st of January and 31st of October of 2016. All variables potentially associated with pre-defined outcomes were studied through logistic regression. The accuracy of the models was assessed by the area under receiver operating characteristics curve and calibration was tested using the Hosmer-Lemeshow goodness-of-fit test.

Results: There were 1804 patients initially selected and 154 of these met the inclusion criteria. Sensitivity to non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole is associated with male gender (adjusted odds ratio (OR) = 2,612) and previous invasive procedures in the last year (adjusted OR = 0,424) (area under receiver operating characteristics (AUROC) curve = 0,65). When considering sensitivity to piperacillin/tazobactam, there was an association with liver disease (adjusted OR = 3,580) and post-operative infections (adjusted OR = 2,944) (AUROC curve = 0,604). Hospital mortality resulted in an association with age ≥ 70 (adjusted OR = 4,677), solid

tumor (adjusted OR = 3,127) and sensitivity to non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole (adjusted OR = 0,368).

Conclusions: In this study, none of the existent classifications had a good discriminative power to identify intra-abdominal infections caused by pathogens sensitive to the current antibiotic treatment recommendations.

Keywords: intra-abdominal infections; classification; antibiotic therapy; hospital mortality.

RESUMO

Introdução: As infeções intra-abdominais representam uma das mais frequentes emergências gastrointestinais e uma importante causa de morbilidade e mortalidade. Uma classificação que inclua todas as caraterísticas das infeções intra-abdominais ainda não existe. Existem duas classificações utilizadas para subdividir infeções intra-abdominais: não complicada ou complicada, considerando a extensão da infeção, e adquirida na comunidade, associada a cuidados de saúde ou adquirida no hospital, baseando-se no local de aquisição. A adequação da antibioterapia empírica inicial prescrita é fundamental. Existe evidência que antibioterapia inadequada e/ou extemporânea está associada com insucesso terapêutico e mortalidade aumentada.

Objetivos: Determinar o impacto das diferentes classificações de infeção intra-abdominal na seleção da melhor antibioterapia empírica. Os objetivos principais do estudo são: identificar fatores independentes para infeção intra-abdominal por microrganismos sensíveis à antibioterapia recomendada para infeções intra-abdominais adquiridas na comunidade: cefalosporina não anti-pseudomónica ou ciprofloxacina mais metronidazol (espectro mais curto e objetivo principal) ou piperacilina/tazobactam; descrever o perfil microbiológico associado a cada classificação; determinar o poder discriminativo de cada classificação na identificação de pacientes infetados por patogéneos sensíveis à antibioterapia elegida; e descrever os fatores de prognóstico associados à mortalidade hospital na população de doentes com infeção intra-abdominal.

Metodologia: Estudo de coorte retrospetivo incluindo todos os pacientes adultos diagnosticados com infeção intra-abdominal, à data de alta, entre 1 de janeiro e 31 de outubro de 2016. Todas as variáveis potencialmente associadas com os desfechos pré-definidos foram analisadas através de regressão logística. A precisão dos modelos foi estudada através da área debaixo da curva característica de operação do recetor e a calibração foi testada pelo teste de Hosmer-Lemeshow.

Resultados: Inicialmente foram selecionados 1804 pacientes e, destes, 154 apresentaram critérios de inclusão. A infeção intra-abdominal por patogéneos sensíveis ao esquema de antibioterapia, cefalosporina não anti-pseudomónica ou ciprofloxacina mais metronidazol, foi associada de forma independente ao sexo masculino (odds ratio (OR) ajustado = 2,612) e a procedimentos invasivos no último ano (OR ajustado = 0,424) (area under receiver operating characteristics (AUROC) curve = 0,65). Quando testada a sensibilidade a piperacilina/tazobactam, existiu uma associação independente com a doença hepática (OR ajustado = 3,580) e as infeções pós-operatórias (OR ajustado = 2,944) (AUROC curve = 0,604). A mortalidade hospitalar associou-se de forma independente com a idade ≥ 70 (OR ajustado = 4,677), tumores sólidos (OR ajustado = 3,127) e

à sensibilidade a cefalosporina não anti-pseudomónica ou ciprofloxacina mais metronidazol (OR ajustado = 0,368).

Conclusões: Neste estudo, nenhuma das classificações existentes teve um bom poder discriminativo na identificação de infeções intra-abdominais causadas por microrganismos sensíveis à antibioterapia atualmente recomendada.

Palavras-chave: infeções intra-abdominais; classificação; antibioterapia; mortalidade hospitalar.

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ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
APACHE-II	Acute Physiology and Chronic Health Evaluation II
ASC	Active Surveillance Culture
ASP	Antimicrobial stewardship programs
AST	Active Surveillance Testing
ATB	Antibiotic
AUROC	Area under receiver operating characteristics
CA-IAI	Community-acquired Intra-abdominal Infection
CCI	Charlson Comorbidity Index
CDC	Centre for Disease Control and Prevention
$CI_{95\%}$	95% Confidence interval
cIAI	Complicated intra-abdominal Infection
DR	Drug-resistant
EC	European Community
ESBL	Extended-spectrum betalactamase
EU	European Union
HA-IAI	Hospital-acquired intra-abdominal infection
HCA-IAI	Healthcare-associated intra-abdominal infection
IAI	Intra-abdominal infection
ICD-9	International Statistical Classification of Diseases and Related Health Problems 9th revision
IQR	Inter-quartile range
KPC	*Klebsiella pneumoniae* carbapenemases
KPS	Karnofsky Performance Status Scale
MDR	Multidrug-resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
OR	Odds ratio
ROC	Receiver operating characteristics
SD	Standard deviation
SMART	Study for Monitoring Antimicrobial Resistance
SPSS	Statistical Package for the Social Sciences
uIAI	Uncomplicated intra-abdominal infection
USA	United States of America
WHO	World Health Organization

INTRODUCTION

Intra-abdominal infections: definition and impact

Intra-abdominal infections (IAIs) include a large diversity of pathological conditions involving inflammatory processes and lesions of all the intra-abdominal organs in response to microorganisms, which may spread into the peritoneal space.[1-5] They include inflammation of single organs (such as cholecystitis, appendicitis, diverticulitis, cholangitis, pancreatitis, salpingitis, etc.), peritonitis (classified as primary, secondary or tertiary) and intra-abdominal abscesses (classified by their location and anatomic configuration).[1, 2, 4, 6]

IAIs represent one of the most frequent gastrointestinal emergencies and a serious cause of morbidity and mortality, especially identified as a cause of severe sepsis in patients in the intensive care unit and the second most common cause of infection-related mortality.[2, 5, 7-10]

Centre for Disease Control and Prevention's definition and criteria

According to the Surveillance Definitions for Specific Types of Infections of Centre for Disease Control and Prevention (CDC), IAIs must match at least one of the following criteria:

- Identification of organisms from an abscess or purulent material from intra-abdominal space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST);
- Patient has abscess or other evidence of IAI on gross anatomic or histopathologic exam;
- Patient has at least two of the following signs or symptoms: fever (>38.0°C), nausea, vomiting, abdominal pain, or jaundice, with no other recognized cause. And at least one of the following:
    - organisms seen on Gram stain or identified from drainage or tissue obtained during invasive procedure or from an aseptically-placed drain by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment;
    - organisms identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment and imaging test evidence suggestive of infection, which if equivocal is supported by clinical correlation (i.e., physician documentation of antimicrobial treatment for intraabdominal infection).[11]

Classifications of intra-abdominal infection

A broad diversity of patient population is described by the term IAI and a full classification that includes all facets of IAIs does not exist.

An optimal classification designed for clinicians' guidance in treatment should include: the origin of the source of infection, the anatomical extension, the supposed pathogens involved and risk factors for major resistance patterns, and the clinical condition of the patient.[3, 5, 10]

Uncomplicated versus complicated intra-abdominal infections

IAIs are most frequently subdivided as uncomplicated or complicated, which is often used in guidelines and clinical trials, and this classification is founded on the extent of infection.[1-6, 10, 12]

An uncomplicated intra-abdominal infection (uIAI) is an infection that only involves a single organ and does not extend to the peritoneum, occurring intramural inflammation of the gastrointestinal tract without anatomic disruption.[1-6, 8-10, 12-14] Patients with this type of infection can be managed with surgical procedures or antibiotic therapy. Acute diverticulitis, acute cholecystitis and some acute appendicitis are examples of uncomplicated intra-abdominal infections that can be managed non-operatively, using antibiotic therapy,[4] but if not properly treated, have an important chance of evolving into a complicated intra-abdominal infection (cIAI). [14]

In situation of a cIAI, the infectious process extends beyond a single organ into the peritoneal space, causing peritoneal inflammation, and is associated with localized or diffuse peritonitis.[1-6, 8-10, 12-14] The treatment of this type of infections should include both surgical and antibiotic therapy.[4, 12]

Localized peritonitis is frequently revealed as an abscess, containing tissue debris, bacteria, neutrophils, macrophages and exudative fluid enclosed in a fibrous capsule. Diffuse peritonitis is afterwards classified as primary, secondary or tertiary peritonitis.[1-6, 8-10, 12]

Primary, secondary and tertiary peritonitis

Peritonitis is an infection in which the local inflammatory process is provoked by microorganisms and can be compared to a sepsis located in the peritoneum.[1] It is universally accepted to classify peritonitis as primary, secondary or tertiary.

Primary peritonitis, additionally known as spontaneous bacterial peritonitis, is a diffuse bacterial infection, commonly with mono-microbial etiology, with maintenance of integrity of the gastrointestinal tract. The infectious process is thought to be the result of bacterial translocation

across an intact gastrointestinal tract and it is regularly detected in cirrhotic patients with ascites, patients with an indwelling peritoneal dialysis catheter and in infancy and early childhood.

Secondary peritonitis is caused by microbial contamination through a perforation, laceration, or necrotic segment of the gastrointestinal tract, and it represents more than 90% of all cases of peritonitis. The etiology of the infection is frequently poly-microbial and dependent on the source of contamination. Anastomotic dehiscences are common causes of peritonitis in the postoperative period.[1, 2, 6, 10] Secondary peritonitis with severe sepsis or septic shock have reported an average associated mortality rate of approximately 30%.[15-18]

Tertiary peritonitis is described as a recurrent or persistent infection of the abdominal cavity that lasts more than 48 hours after allegedly successful and appropriate surgical source control of a secondary peritonitis. It occurs more frequently in critically ill or immunocompromised patients, and is repeatedly linked to highly resistant pathogens and high morbidity and mortality.[1, 2, 6, 10] Despite the common use of the term tertiary peritonitis, it reproduces an evolution and complication of secondary peritonitis, consequently the term "ongoing peritonitis" may be a better classification for this entity.[3, 10]

Community-acquired, hospital-acquired and healthcare-associated intra-abdominal infections

For the sake of a better identification of the pathogens presented and evaluation of related resistance patterns, infections are classically divided in community- or hospital-acquired.[10, 13, 19, 20]

A community-acquired intra-abdominal infection (CA-IAI) is an infection present at hospital admission or within 48 hours in patients that did not meet the criteria for healthcare-associated infection and it is usually caused by the patient's own flora, including *Enterobacteriacea*e, viridans group *Streptococcus* and anaerobes (particularly *Bacteroides fragilis*).[4, 7, 10, 13, 14, 19, 20]

Hospital-acquired intra-abdominal infections (HA-IAIs) are defined as infections that were not present at the time of hospital admission but emerge as noticeable after at least 48 hours in patients hospitalized for other purpose than IAIs[13, 20-22] and are provoked by nosocomial microorganisms of specific hospital or unit.[19]

In the last two decades due to the massive development of the outpatient clinical care, the addition of a new class was proposed named healthcare-associated infections (HCA-IAIs), for the group of infections emerging in patients at the community setting with a recent history of exposure to professional healthcare that do not meet the criteria for HA-IAI.[23, 24]

HCA-IAIs are defined as infections present at hospital admission or within 48 hours of admission in patients with previous contact with healthcare, namely invasive procedures, or that resides in a long-term care facility.[13, 23]

This new classification is far from being consensual and several risk factors have been proposed to be part of it.[10, 14, 23] The most accepted criteria includes: intravenous therapy took at home, wound treatment or specialized nursing care through a healthcare agency, family or friends; or had self-delivered intravenous medical therapy within 30 days previous to the infection; attendance to an hospital or hemodialysis clinic or receiving intravenous chemotherapy received 30 days before; being hospitalized in an acute care hospital for at least 2 days in the past 90 days; or inhabited in a nursing home or long-term care facility.[10, 23, 24]

Lately recent invasive procedures, hospitalization in the last year and previous antibiotic therapy have been increasingly recognized as major risk factors for infection by resistant pathogens among patients arriving from the community with infection.[23]

HCA-IAIs are frequently motivated by higher resistant pathogens, including non-fermenting gram-negative *Pseudomonas aeruginosa* and *Acinetobacter* species, broad spectrum β-lactamase-producing *Klebsiella* species and *Escherichia coli*, *Enterobacter* species, *Proteus* species, methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterococci.[13, 14, 20, 25-27] In these cases, complex multidrug antibiotic therapies are suggested, considering that competent empiric therapy seems to be valuable in affecting postoperative complications and mortality.[13, 14, 25]

Antibiotic therapy that neglect to reach possible pathogens in IAIs has been correlated to greater treatment failure and mortality,[14, 25] being extremely important to choose an antibiotic suited to the most probable pathogens according to the individual patient risk factors, including local flora at the facilities where the patient has acquired the infection.[13]

Treatment of intra-abdominal infections

The intervention needed to treat the infection is conditioned by the anatomical location, the extent of peritoneal inflammation, the established septic reaction, the patient's co-morbidities and the accessible assets of the treatment centre.[4] The success of IAIs' treatment depends on quick and adequate source identification, control and antibiotic therapy.[2, 10, 28]

Source control is any procedure or succession of procedures that remove infectious foci, contain elements that support current infection, and regulate or contain anatomic irregularities to fix normal physiologic function.[2, 6, 10, 14, 29] The failure of it is more expected in patients with postponed procedures (> 24 hours), greater gravity of illness (APACHE-II score ≥ 15), higher age (> 70 years), previous co-morbidities, poor nutritional condition, and a greater extent of peritoneal involvement.[14]

IAIs, such as diverticulitis and some types of acute appendicitis, can be handle without a surgical procedure. Patients treated without a surgical procedure have a microbiology identical to patients treated operatively, and the same antibiotic therapy advocated for patients with cIAIs is

proposed.[14]

The initial empirical antibiotic therapy prescribed for IAIs is an essential need,[2, 4, 10, 12, 13, 20] due to the minimum 48 hours' time required to have microbiological data available (culture and susceptibility results). The empirically planed antibiotic regimen is determined by the intrinsic severity of infection, the microorganisms assumed to be implicated, and the presence of risk determinants suggestive of significant resistance patterns.[2, 4, 10, 12] Suitable empiric antibiotic therapy has a huge impact on the outcome of patients diagnosed with IAIs.[13, 18, 20, 28, 30]

IAI can be managed with single or combined antibiotic regimens, determined by the spectrum demands of antibiotic scope.[4, 5, 10, 31] Ampicillin/sulbactam, cefoxitin, ertapenem, meropenem, moxifloxacin, ticarcillin/clavulanic acid and tigecycline are examples of antibiotic therapy licensed to be used as single agents.[10, 14, 31] Third/fourth-generation cephalosporin (cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone) plus an anti-anaerobe, cefuroxime plus metronidazole, ciprofloxacin plus metronidazole, aztreonam plus clindamycin and aminoglycosides (amikacin, gentamicin, netilmicin, tobramycin) plus an anti-anaerobe are examples of antibiotic therapy used as combination regimens.[10, 31]

Infections originating at the stomach, duodenum, biliary system and proximal small bowel include gram-positive and gram-negative aerobic and facultative pathogens. Infections originating at distal small bowel perforations include gram-negative facultative and aerobic pathogens with diverse quantity. IAIs originating at colon shelter facultative and constrain anaerobic pathogens. In addition, streptococci, especially the *Streptococcus milleri* group, and Enterococci are usually present. The most consistently discovered gram-negative facultative pathogen is *Escherichia coli*.[2, 6, 14, 32]

Anticipating the microorganisms and promising resistance patterns of a particular infection initiates by determining the place of acquisition of the infection[4, 13] (community-acquired, healthcare-associated or hospital-acquired).

In CA-IAI, antibiotics with a restricted spectrum of activity,[4, 10, 13, 31] less expensive and less toxic are suggested,[4, 31] such as second-generation cephalosporins with anaerobic coverage, ampicillin/sulbactam and ticarcillin/clavulanic acid.[13, 31] Antibiotic therapy regimens like cephalosporins without *Pseudomonas aeruginosa* coverage plus metronidazole, ciprofloxacin plus metronidazole, and piperacillin/tazobactam are recommended for the treatment of CA-IAIs.[4, 10, 13, 33] Nevertheless, if CA-IAI patients have previous exposure to antibiotic therapy or severe co-morbidities involving simultaneous antibiotic therapy, anti-ESBL-producer coverage may be ensured. Conversely, in HA-IAIs, antibiotic regimens with vaster spectra of coverage are suggested.[4, 10, 12]

There were reported, in past decades, an augmented prevalence of IAIs caused by antibiotic-resistant pathogens,[4, 10, 13] such as MRSA, vancomycin-resistant *Enterococcus* species, carbapenem-resistant *Pseudomonas aeruginosa*, extended-spectrum betalactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species, and multidrug-resistant *Acinetobacter* species.[4, 10, 34, 35]

Cultures are strongly recommended, particularly in patients at risk for infection by drug resistant (DR) pathogens, for consequent antibiotic therapy adjustment, aiming at maximizing its effect in the involved pathogens while minimizing selective pressure.[4, 7, 10] This is particularly in HCA-IAIs and HA-IAIs in which the antibiotic susceptibility testing is endorsed to adjust empirical antibiotic therapy.[7, 25, 36]

Even though it has been recorded that bacteriological cultures have minor influence on the progress of treatment of frequent diseases like appendicitis, in this period of extensive DR pathogens implicated in hospital and community-acquired infections, the danger of resistance is a cause of leading apprehension that cannot be neglected.[4, 10]

Resistance to antibiotic therapy

In various regions, there is an emerging resistance to elected antibiotics among community-acquired strains of gram-negative pathogens, including a broad predominance of ampicillin/sulbactam-resistant *Escherichia coli* globally, fluoroquinolone-resistant *Escherichia coli* in Latin America and East Asia, and regions with grand prevalence of enhanced-spectrum β-lactamase-producing strains of *Klebsiella* species and *Escherichia coli*.[14, 37] A relatively greater predominance, in some populations and communities, of more-resistant non-enteric gram-negative pathogens, such as *Pseudomonas aeruginosa*, will influence the choice of suitable empiric antibiotic therapy.[10, 14]

This has led to the recommendation that when 10-20% or more isolates from a usual community intra-abdominal pathogen shows resistance to a specific antibiotic, its use should be refrained.[14]

The range of pathogens implicated in hospital-acquired infections is much vaster. In the past two decades, the prevalence of hospital-acquired infections caused by DR pathogens has raised seriously, perhaps in relation with the rising levels of antibiotic exposure and escalating recurrence of patients with co-morbidities, such as augmented severity of chronic illness, higher age, extension of organ injury, low albumin levels, poor nutritional state, immunodepression and the existence of malignancy.[4, 13] Infections by resistant pathogens, especially hospital-acquired are associated with increased risk of treatment failure and death.[25, 38-40]

Even though the transmission of multidrug-resistant (MDR) pathogens is most usually detected in acute care facilities, all healthcare environments are disturbed by the development of DR microorganisms.[4]

Risk factors, such as prior antibiotic therapy (for more than 48 hours in the previous two weeks) or during the prior three months, hospital stay's duration or reoperation hiatus greater than five days, were linked to the development of IAIs by MDR pathogens.[7, 41, 42]

Furthermore, the major resistance issue of IAIs is presented by ESBL-producing

Enterobacteriaceae that are dangerously widespread in HA-IAIs and regularly noticed in CA-IAIs, even if in a lower frequency.[4, 7, 10, 13]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored the *in vitro* susceptibility patterns of clinical Gram-negative bacilli to antimicrobial agents collected worldwide from IAIs since 2002. Hawser *et al.* described an increase in resistance rates of intra-abdominal pathogens in Europe and the consequent decline of the number of available alternatives for the empirical treatment of IAIs.[4, 43]

Even if a diversity of factors can boost the danger of selection for ESBL producers, the most important determinants involve previous antibiotics' exposure (particularly third generation cephalosporins) and co-morbidities involving simultaneous antibiotic therapy.[4, 6, 13]

Bacteria generating *Klebsiella* pneumoniae carbapenemases (KPCs) are quickly arising as a main origin of multi-resistant infection around the globe.[4, 10] The late rise of carbapenem resistance in association with *Enterobacteriaceae* present a significant danger to hospitalized patients and a real challenge for clinical treatment.[4]

Along with hydrolyzing carbapenems, KPC-producing strains are frequently resistant to diverse alternative antibiotics, and competent treatment of these adaptable microorganisms has accordingly evolve into a serious obstacle for clinicians in acute care settings.[4] KPC-producing bacteria have become prevalent in hospital-acquired infections, particularly in patients with prior exposure to antibiotics.[4]

Moreover, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have presented disquieting rates of expanded resistance to diverse antibiotics in hospitals and healthcare facilities around the world. Both pathogens are naturally resistant to various antibiotics and can acquire supplementary resistances to alternative valuable antibiotics.[4, 6, 10]

In the class of MDR gram-positive bacteria, Enterococci last a substantial challenge[4]. Empirical coverage of *Enterococci* is not advocated in CA-IAIs.[4, 6, 7, 13, 31] Studies have proved that coverage facing Enterococci provides minor therapeutic advantage.[4, 31]

MRSA is another MDR gram-positive nosocomial microorganism acknowledged to induce serious morbidity and mortality around the world.[4, 6]

Even though community-acquired MRSA has been noted in other placings, there are no systematic data recorded in studies supporting the presence of MRSA in CA-IAIs.[4, 10, 44]

HA-IAIs should not be managed empirically for MRSA excepting in patients with record of past infections by this pathogen or in case of considering that the infection is related to MRSA.[4, 6]

Consequences of antibiotics misuse

There is evidence that inadequate and/or delayed antibiotic therapy is associated with treatment failure and increased mortality.[2, 13, 14, 18, 25, 28, 30, 45-49]

The sensitive equilibrium between the enhancement of empirical antibiotic therapy, which was proved to promote better clinical results, and the decline of needless antimicrobial overuse, which has been linked to the increasing development of MDR pathogens, is invariably needed when treating infections.[10, 13, 50]

Furthermore, needless wide coverage and excessively extended antibiotic therapy is associated with patient- and agent-specific toxicities of therapy, as well as superinfection by *Clostridium difficil*e and organ damage.[6, 8, 10, 14, 51]

The use of antibiotics impacts not only the individual recipient, but also others that may be colonized or infected by resistant bacteria.[50, 52] The gain of constitutionally resistant pathogens and selective pressure for resistance in the unit, hospital or community is of rising consideration.[10, 14, 31, 53, 54] It was considered a major public health issue and a danger for the future of healthcare by the World Health Organization (WHO) and the European Community (EC).[18, 50, 52, 55-57]

The main promoter of antibiotic resistance is the selective pressure induced by the use of antimicrobials, being the antibiotic overuse in humans and food-producing animals the major causes.[56] Discoveries suggest that 80% of all antimicrobial are intended for food-producing animals, advocating for a better surveillance of agricultural and veterinary practises.[56, 58]

Antibiotic use in food animal production is frequent in several countries, including the United States of America (USA), where there is no control of antibiotic use in food-producing animals. European Union (EU) banned the use of nontherapeutic antibiotics of human importance to farm animals in 2006.[55, 56]

There is an essential need to develop new antimicrobial agents for the treatment of patients given the colonization of hospitalized patients with resistant microorganisms.[31, 50] Since 1987, there have been no effective discoveries of new antibiotic classes.[56]

Due to the limited development of new antibiotics, particularly for gram-negative microorganisms, the careful use of antibiotic therapy is essential to hold the resistance rates and preserve the existent antibiotics.[10, 52, 55, 57]

Antimicrobial stewardship programs (ASP) can promote a better use of antibiotic therapy, de-escalation and reduce unsuitable prolonged durations of treatment,[8, 18] being vital to hold and control resistance.[10, 52, 57] They are also important to promote public understanding of the danger of antimicrobial resistance.[52, 56]

In light of the promising complexity of choosing suitable antibiotic therapy, local and regional protocols must be settled on the support of community root, patient comorbidities, clinical severity, existence of recorded beta-lactam allergy and by assessing local bacterial resistance data, which must

be developed by multidisciplinary teams (anesthetists-intensive care physicians, microbiologists, surgeons, infectious disease specialists and pharmacists).[7, 8] Published articles have proven an improvement in antibiotic prescription practices after the implementation of antibiotic prescription protocols.[18, 56, 59]

The misuse of antibiotics is a leading worldwide issue with an extensive economic influence on rising healthcare costs, due to the selection of MDR bacteria, culminating in extended hospital stay and a greater mortality, improving its use would probably lead to lower costs and better outcomes.[4, 5, 10, 12, 30, 52]

STUDY AIMS AND OBJECTIVS

This study was designed to assess the impact of the different classifications of IAIs in the selection of the best antibiotic therapy, considering the need of adequate empirical antibiotic therapy and public health need to preserve antibiotics.

The main objectives of the study are:

- to identify independent risk factors for IAI by pathogens sensitive to the antibiotic scheme recommended for CA-IAI: non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole or piperacillin/tazobactam;
- to describe the microbiological profile associated with each classification;
- to determine the discriminative power of each IAI classification to identify patients infected by a pathogen sensitive to the shorter spectrum antibiotic combination (non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole);
- to describe major prognostic factors associated with hospital mortality among the study population of patients with IAI.

MATERIALS AND METHODS

Retrospective cohort study developed at Hospital de Santo António, Centro Hospitalar do Porto, a tertiary care university hospital, including all adult patients (≥ 18 years old) discharged from the hospital with the diagnosis of IAI between 1st of January and 31st of October of 2016.

The study was approved by the local ethics committee (ref. 2017.226(195-DEFI/187-CES).

First selection of the patients was achieved using the International Statistical Classification of Diseases and Related Health Problems 9th revision (ICD-9) (appendix A). For selected patients, clinical file was reviewed to confirm inclusion criteria and data of interest retrieved (appendix B).

Exclusion criteria were: patients with anal/rectal pathology, infections caused by non-bacterial pathogens (that is virus, fungus and protozoa), non-complicated appendicitis, tuberculosis and patients with negative or no culture results.

The following variables were collected: age, gender, functional status, previous comorbidities, hospital admission date, discharge date, place of acquisition of the infection (community-acquired, healthcare-associated or hospital-acquired), extent of infection (uncomplicated or complicated), localization of infection (appendix, biliary tract, colon, small intestine, stomach/duodenum or other), post-operative infection (perforation, suture dehiscence, tertiary peritonitis, undetermined or non-applicable), microorganism(s) isolated, location of the isolated pathogen, realization of blood cultures, blood cultures' result, resistance of isolated pathogens, empirical therapy administered to the patient in the first 24 hours after diagnosis (antibiotic, daily dose, route of administration), change of the initial antibiotic therapy, reason of the changing, adequacy of the empirical antibiotic therapy, risk factors for healthcare-associated infections, previous colonization/infection by DR pathogen, previous antibiotic therapy (last 3 months), previous hospital admission (last year), previous invasive procedures (last year) and residence in a long-term care facility or nursing home and outcome at hospital discharge (dead or alive).

Functional status was assessed by the Karnofsky Performance Status Scale (KPS)[60] and previous comorbidities by the Charlson Comorbidity Index (CCI)[61]. The initial empirical antibiotic therapy was considered appropriate if all of the bacteria isolated from cultures were sensitive to at least one of the drugs administered.

The primary outcome of interest was infection by a pathogen sensitive to the following antibiotic scheme: non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole. Secondary outcomes were sensitivity to piperacillin/tazobactam and hospital mortality.

Statistical analysis

Data were described with means and standard deviations (SD) for continuous variables or with medians and inter-quartile ranges (IQR) if they showed a skewed distribution. Categorical variables were described with absolute frequencies and percentages. T-tests or Mann-Whitney-U tests were used to compare continuous variables. For categorical variables, these comparisons were performed using Pearson χ^2 and Fisher's exact tests.

All variables potentially associated with pre-defined outcomes were studied through logistic regression. Those with a clear association in the univariate analysis ($p < 0.1$) were included in the multivariable analysis. The results of the multivariable models are expressed as odds ratio (OR) with 95% confidence interval ($CI_{95\%}$) and p-values. The accuracy of the models was assessed by the area under receiver operating characteristics (AUROC) curve and calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The significance level was defined as $p < 0.05$.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

There were 1804 patients discharged from the hospital during the study period that met the ICD-9 established criteria. Of these, 154 met the inclusion criteria (figure 1).

Patient and hospitalization characteristics

The 154 patients included in the study had a mean±SD age of 73±14 years and 52% were female; 112 (73%) need some help for daily activities defined by a KPS score < 70 and 31 (20%) patients had no comorbidities according to the CCI definitions (table I).

Median (IQR) hospital length of stay was 17 (10-29) days and hospital mortality rate was 22% (n=34).

The following risk factors were associated with an IAI by pathogens sensitive to the recommended shorter spectrum antibiotic therapy (non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole): male gender, previous antibiotic therapy and previous invasive procedures (table I).

In the multivariable analysis with the following antibiotic combination: non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole as the dependent variable, the final model retained male gender with an adjusted OR ($CI_{95\%}$) = 2,612 (1,328-5,148) and previous invasive procedures in the last year with an adjusted OR ($CI_{95\%}$)= 0,424 (0,216-0,833). The area under the receiver operating characteristics (ROC) curve ($CI_{95\%}$) was 0,65 (0,57-0,74) (table II).

With piperacillin/tazobactam as the dependent variable, the multivariable analysis retained liver disease with an adjusted OR ($CI_{95\%}$) = 3,580 (1,126-10,879) and post-operative infections with an adjusted OR ($CI_{95\%}$) = 2,944 (1,096-7,908). The area under the ROC curve ($CI_{95\%}$) was 0,604 (0,504-0,704) (table II).

Intra-abdominal infections classification and microbiological results

In table III, the distribution of IAI according to different classifications along with the associated microbiological profile is shown.

Post-operative infection was observed in 19 (12%) patients, caused by suture dehiscence in 8 (5%) patients, perforation in 3 (2%) patients and undetermined or by other causes in 8 (5%) patients.

Blood cultures were drawn in 122 (79%) patients, of those 69 (45%) were positive. Besides blood, pathogens were isolated from peritoneal fluid in 60 (39%), bile in 13 (8%), feces in 11 (7%), abscess in 9 (5%), biliary drainage fluid in 1 (1%) and pancreas drainage fluid in 1 (1%)

Antibiotic therapy

Although non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole is the shorter spectrum recommended antibiotic therapy for CA-IAI, it was administered to only one patient, but if it was administered to all patients, it would have been adequate in 54% of them.

Among the antibiotic agents administered, piperacillin/tazobactam was the most frequently used, in 123 (80%) patients, followed by metronidazole in 7 (5%) patients, imipenem plus cilastatin in 6 (4%) patients, ciprofloxacin in 5 (3%) patients and amoxicillin/clavulanic acid in 4 (3%) patients. Nevertheless, the sensitivity to piperacillin/tazobactam was exhibited in 105 (68%) patients.

The distribution of sensitive pathogens to the studied antibiotic regimens (non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole, or piperacillin/tazobactam), according to the different classifications is shown on table III.

The empirical antibiotic therapy was changed in 83 (54%) patients, of these the susceptibility profile of the isolated pathogen was the most frequent reason in 40 (48%) patients.

The initial antibiotic therapy was adequate in 98 (64%) patients: 60 (72%) with CA-IAIs, 26 (56%) with HCA-IAIs and 12 (46%) with HA-IAIs (p=0,034). In uIAI, 17 (68%) patients had adequate initial antibiotic therapy and in cIAI 81 (63%) patients had it (p=0,620). There was no relation between the local of infection and the adequacy of the initial antibiotic therapy (p=0,628).

In patients with post-operative infections, a higher frequency of inadequate antibiotic therapy was observed (63% vs 33%, p=0,010).

Prognostic risk factors in intra-abdominal infections

In the multivariable analysis with the hospital mortality as the dependent variable, the final model retained age ≥ 70 with an adjusted OR ($CI_{95\%}$) = 4,677 (1,260-17,358), solid tumor with an adjusted OR ($CI_{95\%}$)= 3,127 (1,183-8,266) and sensitivity to non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole with an adjusted OR ($CI_{95\%}$) = 0,368 (0,138-0,980).

Factors significantly associated with hospital mortality were: KPS score <70, chronic kidney disease, the total score of CCI, localization of infection, polymicrobial flora and sensitivity to non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole (table IV).

DISCUSSION

The main finding of our study was the fact that none of the existent classifications had a good discriminative power to identify IAIs caused by pathogens sensitive to the current antibiotic treatment recommendations. This supports the poor utility of the existent classifications of IAI.

Independent risk factors for IAI caused by those pathogens was male gender, for which we cannot found an explanation or similar results in other published studies; and previous invasive procedures in the last year which were associated with IAI by pathogens not sensitive to the shorter antibiotic scheme recommended for CA-IAI, which has also been enlightened by other studies that linked previous invasive procedures with greater rates of colonization and infection with MDR pathogens.[23]

An alternative antibiotic scheme for CA-IAI is piperacillin/tazobactam, which is an antibiotic with a broader spectrum. Post-operative infections were associated with a higher sensitivity to this antibiotic therapy. This result cannot be explained by this study or the literature reviewed. Liver disease also showed an association with increased sensitivity to this antibiotic therapy. Sargenti *et al.*[62] revealed that patients with liver disease have mainly HCA-IAIs and HA-IAIS, which are often caused by bacteria resistant to commonly used antibiotics, piperacillin/tazobactam might be an option for this group of patients.[63]

The fact that the discriminative power of the developed models based on the patient's individual characteristics presented a better discriminative power than existing classifications of IAI suggests that a new classification that also includes patient's individual risks would be more helpful for choosing initial antibiotic therapy adequately.

Our data reveled that age≥70 years was associated to an increased hospital mortality, which is also supported by the conclusions of other studies.[20] Higher age was also connected, by many studies, to a greater prevalence of DR pathogens, which has been implicated in an augmented mortality rate.[38-40] Solid tumor was the one comorbidity that presented a connection with greater mortality, which can be clarified by the higher prevalence of DR pathogens that will result in an increased mortality rate.[13, 38-40] Patients with pathogens sensitive to non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole had an associated lower hospital mortality, in this study. This antibiotic scheme recommended for community-acquired infections is the shortest spectrum one, pathogens sensitive to this regimen are less resistant, having adequate antibiotic therapy more frequently and causing infection with lower severity, which can explain this association.

The distribution of IAIs according to the place of acquisition was distinctive when compared to various studies, in which the proportion of CA-IAIs fluctuated between 33% and 87%, and the ratio of HA-IAIs or HCA-IAIs oscillated between 13% and 67%.[9, 20, 44, 64, 65] This difference can be explained by the fact that the majority of these analyses used a classification that not discriminate CA-IAI, HCA-IAI and HA-IAI, adding HCA-IAIs as part of CA-IAIs or HA-IAIs. In our study, the

discrimination in three instead of two groups of IAIs according to the place of acquisition presented a better performance, particularly when considering IAIs by pathogens sensitive to piperacillin/tazobactam.

A study by Swenson *et al.*[65] recognized that colorectal (26,4%), liver or biliary (25,5%) and small bowel (18,1%) were the most common location of IAIs, which is different in proportion when compared with our study, but establishes consonance in the two most frequent locals (biliary tract and colon).

Previous antibiotic therapy was recognized in 25% of patients with cIAI, which is similar to the percentage observed by Huang *et al.*[9] (27%).

The total score of CCI was associated with increased hospital mortality in accordance with the study by Montravers *et al.*[20], that also revealed that the presence of one or more comorbidities had a predictive value for hospital mortality.

In our study, most of the patients had blood cultures taken (79%) and nearly half were positive (45%), which is similar to the results of Krobot *et al.*[28] (43%), but considerably higher than the data observed by Montravers *et al.*[20] (6%). Microbiological cultures, including blood cultures, in IAIs are extremely important to establish an adequate antibiotic therapy and should be collected in every patient with IAI.[4, 7, 13]

The distribution of isolated pathogens, in our study, was identical to other reports, being *Escherichia coli* the most frequent independently of the classification used.[9, 20, 28, 44, 64, 66] The prevalence of monomicrobial IAIs (62%) was much superior by comparison to the studies by Claridge *et al.*[66] (41%) and Shah *et al.*[67] (33%).

A study by Montravers *et al.*[20] noticed that amoxicillin plus clavulanic acid was the most frequent antibiotic therapy administered to patients with CA-IAIs and one of the two antibiotic therapies (in addition to piperacillin plus tazobactam) used in patients with nosocomial IAIs. This data contrasts with our study results, in which piperacillin plus tazobactam was the most frequent antibiotic therapy administered (80%) and amoxicillin plus clavulanic acid was used in 3% of patients with IAIs.

The antibiotic therapy adequacy results of our study were distinctive from the identified by Montravers *et al.*[20]: 72% vs 63% in patients with CA-IAIs; 56% in patients with HCA-IAIs and 46% in patients with HA-IAIs vs 67% in patients with nosocomial IAIs, respectively. However, the rate of inadequate antibiotic therapy (36%) is within the range described in similar studies: a scope between 13% and 44%.[28]

In our study, there was no significant difference in hospital mortality between adequate and inadequate antibiotic therapy, which was also observed by Montravers *et al.*[20], but opposed to other several studies.[9, 14, 25]

The hospital mortality observed in this study is higher than the described by Sartelli *et al.*[44] (22% vs 11%), but comparable to the results presented by Montravers *et al.*[20]: 22% vs 24% in CA-

IAIs; 20% in HCA-IAIs and 27% in HA-IAIs vs 23% in nosocomial IAIs.

Our study has some limitations. Firstly, since it is a single-centered study, the analysis was based on local data and resistance patterns. Being a retrospective study, data collection was limited to the existing records.

Therefore, the results of this study must be interpreted prudently.

We have not found studies that investigated the discrimination of different classifications of IAI on the selection of the best antibiotic therapy, so we assume that our results could be of value to the clinicians on the field.

CONCLUSIONS

In our study, none of the existent classifications helped significantly in the identification of IAIs caused by pathogens sensitive to the current antibiotic treatment recommendations for CA-IAI, which reinforces the poor utility of the existent classifications of IAI.

Probably, a new classification that adds patient's risk factors might have a greater potential in distinguish IAIs by sensitive pathogens allowing a better choice of empiric antibiotic therapy, tailored to individual patients needs with the minimum selective pressure.

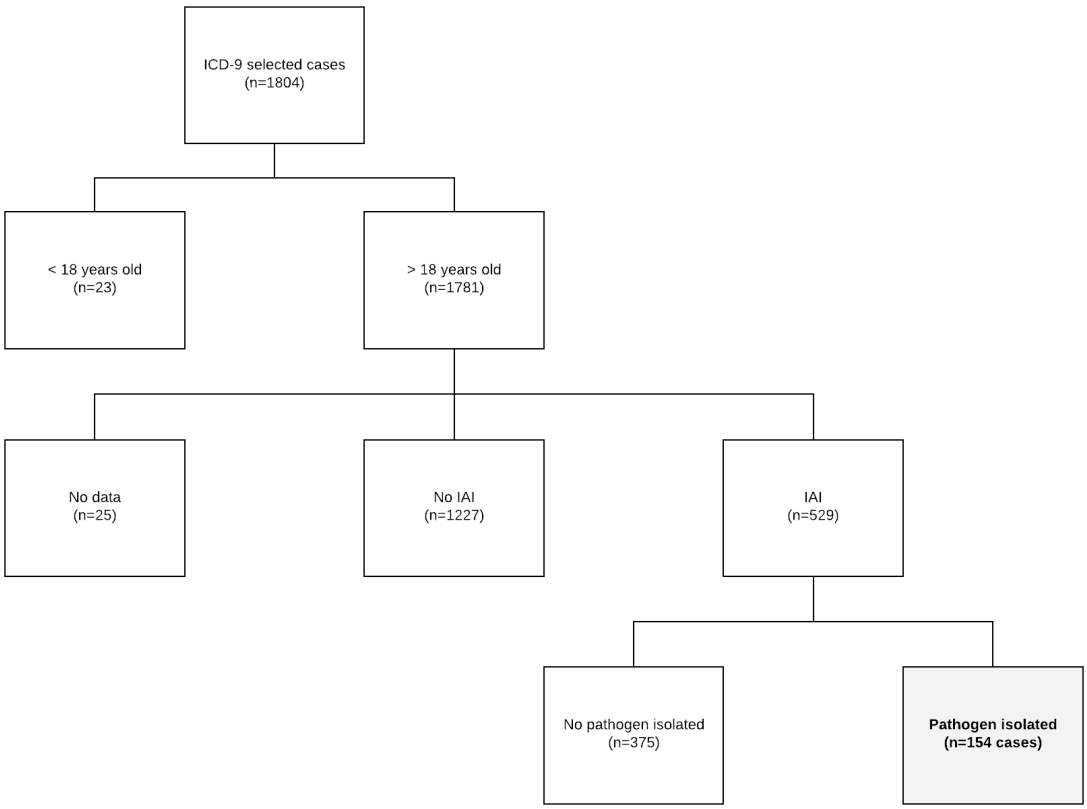

Figure 1. Flow diagram of the population selection process. (ICD-9, International Statistical Classification of Diseases and Related Health Problems 9th revision; IAI, intra-abdominal infection)

Table 1. General characteristics of the study population and risk factors for IAI by pathogens sensitive to the following antibiotic scheme: non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole. (*, Fisher's exact test; AIDS, acquired immune deficiency syndrome; DR, drug-resistant; OR, odds ratio)

	Total	IAI by susceptible pathogens	p value	Crude OR
Age ≥ 70, n (%)	101 (66)	52 (52)	0,874	0,948
Male gender, n (%)	**74 (48)**	**46 (62)**	**0,015**	**2.223**
Karnofsky Performance Status Scale < 70, n (%)	112 (73)	62 (55)	0,167	1,653
Diabetes, n (%)	45 (29)	19 (42)	0,121	0,575
Liver disease, n (%)	14 (9)	6 (43)	0,475	0,669
Solid tumour, n (%)	45 (29)	23 (51)	0,894	0,954
AIDS, n (%)	1 (1)	1 (100)	1,000*	-
Chronic kidney disease, n (%)	26 (17)	9 (35)	0,052	0,425
Congestive heart failure, n (%)	11 (7)	7 (64)	0,537*	1,678
Myocardial infarction, n (%)	10 (7)	7 (70)	0,331*	2,269
Chronic obstructive pulmonary disease, n (%)	10 (7)	6 (60)	0,748*	1,419
Peripheral vascular disease, n (%)	22 (14)	11 (50)	0,843	0,913
Cerebrovascular accident/transient ischemic attack, n (%)	14 (9)	8 (57)	0,683	1,259
Dementia, n (%)	11 (7)	3 (27)	0,120*	0,321
Hemiplegia, n (%)	1 (1)	1 (100)	1,000*	-
Connective tissue disease, n (%)	2 (1)	1 (50)	1,000*	-
Leukemia, n (%)	3 (2)	1 (33)	0,608*	0,456
Malignant lymphoma, n (%)	1 (1)	1 (100)	1,000*	-
Peptic ulcer disease, n (%)	4 (3)	3 (75)	0,621*	2,844
Total score - Charlson Comorbidity Index, mean±SD	5±3	5±3	0.956	0,980 per point
Residence in a long-term care facility or nursing home, n (%)	7 (5)	2 (29)	0,259*	0,349
Previous colonization/infection by DR pathogen, n (%)	29 (19)	16 (55)	0,700	1,173
Previous antibiotic therapy, n (%)	**39 (25)**	**14 (36)**	**0,020**	**0,416**
Previous hospitalization, n (%)	82 (53)	37 (45)	0,070	0,555
Previous invasive procedures, n (%)	**78 (51)**	**34 (44)**	**0,028**	**0,407**
Post-operative Infection, n (%)	19 (12)	9 (47)	0,670	0.811

Table II. Discriminative power of each classification for intra-abdominal infection by pathogen sensitive to antibiotic scheme for treatment of CA-IAI. (AUROC, area under receiver operating characteristics; CI, confidence interval; ATB 1, non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole; ATB 2, piperacillin/tazobactam; CA-IAI, community-acquired intra-abdominal infection; HCA-IAI, healthcare-associated intra-abdominal infection; HA-IAI, hospital-acquired intra-abdominal infection; uIAI, uncomplicated intra-abdominal infection; cIAI, complicated intra-abdominal infection)

Classification of intra-abdominal infection	**AUROC curve (95% CI) for ATB 1**	**p value**	**AUROC curve (95% CI) for ATB 2**	**p value**
Place of acquisition: CA-IAI, HCA-IAI, HA-IAI	0.570 (0.480-0.661)	0.134	0.657 (0.562-0.751)	0.002
Place of acquisition: CA-IAI and HA-IAI	0.540 (0.448-0.632)	0.391	0.586 (0.485-0.686)	0.087
Extent of infection: uIAI or cIAI	0.606 (0.515-0.696)	0.024	0.501 (0.402-0.599)	0.989
Local of infection	0.591 (0.500-0.681)	0.053	0.572 (0.475-0.668)	0.152

Table III. Distribution of IAI according to different classifications and associated microbiological profile. (ATB I, non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole; ATB 2, piperacillin/tazobactam; CA-IAI, community-acquired intra-abdominal infection; HCA-IAI, healthcare-associated intra-abdominal infection; HA-IAI, hospital-acquired intra-abdominal infection; uIAI, uncomplicated intra-abdominal infection; cIAI, complicated intra-abdominal infection)

Place of acquisition, n (%)	CA-IAI, 83 (54)	HCA-IAI, 45 (29)	HA-IAI, 26 (17)
Microbiological profile, n (%)	Monomicrobial, 46 (55) *E. coli*, 19 (41) *Klebsiella* spp., 7 (15) *E. faecium*, 4 (19) Other, 16 (25) Polymicrobial, 37 (45)	Monomicrobial, 32 (61) *E. coli*, 7 (22) *Klebsiella* spp., 7 (22) *Clostridium* spp, 6 (19) Other, 12 (37) Polymicrobial, 13 (29)	Monomicrobial, 17 (65) *E. coli*, 4 (24) *Klebsiella* spp., 2 (12) *E. faecium*, 2 (12) *Clostridium* spp, 2 (12) Other, 7 (40) Polymicrobial, 9 (35)
IAI by pathogens sensitive to ATB I, n (%)	50 (60)	20 (44)	10 (40)
IAI by pathogens sensitive to ATB II, n (%)	66 (80)	27 (60)	12 (46)

Extent of infection, n (%)	uIAI, 25 (16)	cIAI, 129 (84)
Microbiological profile, n (%)	Monomicrobial, 15 (60) *Clostridium* spp, 9 (60) *E. coli*, 2 (13) *E. faecium*, 2 (13) Other, 2 (13) Polymicrobial, 10 (40)	Monomicrobial, 80 (62) *E. coli*, 28 (35) *Klebsiella* spp., 16 (20) *E. faecium*, 8 (10) Other, 28 (35) Polymicrobial, 49 (38)
IAI by pathogens sensitive to ATB I, n (%)	5 (20)	75 (60)
IAI by pathogens sensitive to ATB II, n (%)	17 (68)	88 (68)

Local of infection, n (%)	Biliary Tract, 78 (51)	Colon, 43 (28)	Other, 33 (21)
Microbiological profile, n (%)	Monomicrobial, 54 (69) *E. coli*, 23 (43) *Klebsiella* spp., 13 (24) *E. faecium*, 7 (13) Other, 35 (45) Polymicrobial, 24 (31)	Monomicrobial, 21 (49) *Clostridium* spp, 11 (52) *E. coli*, 3 (14) *E. faecium*, 2 (10) Other, 5 (24) Polymicrobial, 22 (51)	Monomicrobial, 20 (60) Polymicrobial, 13 (40)
IAI by pathogens sensitive to ATB I, n (%)	42 (54)	20 (47)	18 (55)
IAI by pathogens sensitive to ATB II, n (%)	51 (65)	32 (74)	22 (67)

Table IV. Risk factors for hospital mortality. (*, Fisher's exact test; AIDS, acquired immune deficiency syndrome; DR, drug-resistant; OR, odds ratio; ATB I, non-pseudomonal cephalosporin or ciprofloxacin plus metronidazole; ATB 2, piperacillin/tazobactam)

	Total	Hospital mortality	p value	Crude OR
Age ≥ 70, n (%)	101 (66)	27 (27)	0,055	2,398
Male gender, n (%)	74 (48)	13 (18)	0,194	0,599
Karnofsky Performance Status Scale < 70, n (%)	**112 (73)**	**20 (18)**	**0,042**	**0,435**
Diabetes, n (%)	45 (29)	10 (22)	0,978	0,988
Liver disease, n (%)	14 (9)	4 (29)	0,512*	1,467
Solid tumor, n (%)	45 (29)	14 (31)	0,082	2,010
AIDS, n (%)	1 (1)	0 (0)	1,000*	-
Chronic kidney disease, n (%)	**26 (17)**	**10 (39)**	**0,027**	**2,708**
Congestive heart failure, n (%)	11 (7)	0 (0)	0,124*	-
Myocardial infarction, n (%)	10 (7)	1 (10)	0,461*	0,374
Chronic obstructive pulmonary disease, n (%)	10 (7)	3 (30)	0,693*	1,562
Peripheral vascular disease, n (%)	22 (14)	4 (18)	0,785*	0,756
Cerebrovascular accident/transient ischemic attack, n (%)	14 (9)	0 (0)	0,041*	-
Dementia, n (%)	11 (7)	5 (46)	0,066*	3,276
Hemiplegia, n (%)	1 (1)	0 (0)	1,000*	-
Connective tissue disease, n (%)	2 (1)	1 (50)	0,394*	3,606
Leukemia, n (%)	3 (2)	2 (67)	0,123*	7,437
Malignant lymphoma, n (%)	1 (0,6)	0 (0)	1,000*	-
Peptic ulcer disease, n (%)	4 (3)	0 (0)	0,576*	-
Total Score - Charlson Comorbidity Index, mean±SD	**5±3**	**5±3**	**0,045**	**0,866 per point**
Residence in a long-term care facility or nursing home, n (%)	7 (5)	2 (29)	0,469*	1,484
Previous colonization/infection by DR pathogen, n (%)	29 (19)	4 (14)	0,322*	0,507
Previous antibiotic therapy, n (%)	39 (25)	11(28)	0,286	1,571
Previous hospitalization, n (%)	82 (53)	19 (23)	0,727	1,146
Previous invasive procedures, n (%)	78 (51)	18 (23)	0,644	1,200
Post-operative Infection, n (%)	19 (12)	3 (16)	0,483	0,629
Initial antibiotic therapy adequate, n (%)	98 (64)	21(21)	0,797	0,902
Polymicrobial flora, n (%)	**59 (38)**	**18 (31)**	**0,049**	**2,168**
Sensitive to ATB I, n (%)	**80 (52)**	**12 (15)**	**0,030**	**0,417**
Sensitive to ATB II, n (%)	105 (68)	19 (18)	0,084	0,501

Positive blood cultures, n (%)	69 (57)	16 (15)	0,065	0,429
Post-operative infection, n (%)	19 (12)	3 (16)	0,570*	1,590
Place of acquisition – classification, n (%)	154 (100)	34 (22)	0,790	-
Community-acquired, n (%)	83 (54)	18 (22)	-	1,000
Healthcare-associated, n (%)	45 (29)	9 (20)	-	1,330
Hospital-acquired, n (%)	26 (17)	7 (27)	-	1,474
Extent of infection – classification, n (%)	154 (100)	34 (22)	0,195*	-
Uncomplicated, n (%)	25 (16)	3 (12)	-	1,000
Complicated, n (%)	129 (84)	31 (24)	-	2,320

APPENDIX

Appendix A. ICD-9 selected codes

ICD-9 code	Designation
001	Cholera disease
002	Typhoid and paratyphoid fevers
003	Other Salmonella infections
004	Shigellosis
005	Other poisoning (bacterial)
008	Intestinal infections due to other organisms
009	Ill-defined intestinal infections
038.3	Septicemia due to anaerobes
038.4	Septicemia due to other gram-negative organisms
038.8	Other specified septicemias
038.9	Unspecified septicemia
540	Acute appendicitis
562.1	Diverticula of colon
567	Peritonitis and retroperitoneal infections
568.89	Other specified disorders of peritoneum
569.5	Abscess of intestine
569.61	Infection of colostomy or enterostomy
569.83	Perforation of intestine
572.0	Acute and subacute necrosis of liver
574.0	Calculus of gallbladder with acute cholecystitis
574.1	Calculus of gallbladder with other cholecystitis
574.3	Calculus of bile duct with acute cholecystitis
574.4	Calculus of bile duct with other cholecystitis
574.6	Calculus of gallbladder and bile duct with acute cholecystitis
574.7	Calculus of gallbladder and bile duct with other cholecystitis
574.8	Calculus of gallbladder and bile duct with acute and chronic cholecystitis
575.0	Acute cholecystitis
575.1	Other cholecystitis
576.1	Cholangitis
576.3	Perforation of bile duct
577	Diseases of pancreas

Appendix B. Case Report Form

Intra-abdominal Infections (IAIs): the role of different classifications on the selection of the best antibiotic treatment

Case Report Form

Date *(DD/MM/YYYY)*								

Assigned Study Number								

Assigned Study Number - **Completion Instructions**:	
1st space	Initial of Patient's First Name
2nd space	Initial of Patient's Last Name
3rd space	Initial of Hospital Department's Name
4th space	2nd letter of Hospital Department's Name
5th space	Hospital Department Number, when applicable
6th-9th spaces	Case Number counting

1. General information

1. Gender	1		Male	2		Female

2. Hospital admission date *(DD/MM/YYYY)*								
3. Discharge date *(DD/MM/YYYY)*								

2. General Medical Condition

1. Karnofsky Performance Status Scale			
1	**100**	Normal with no complaints; no evidence of disease.	
2	**90**	Able to carry on normal activity; minor signs or symptoms of disease.	
3	**80**	Normal activity with effort; some signs or symptoms of disease.	
4	**70**	Cares for self; unable to carry on normal activity or to do active work.	
5	**60**	Requires occasional assistance, but able to care for most of his personal needs.	
6	**50**	Requires considerable assistance and frequent medical care.	
7	**40**	Disabled; requires special care and assistance.	
8	**30**	Severely disabled; hospital admission is indicated although death not imminent.	
9	**20**	Very sick; hospital admission necessary; active supportive treatment necessary.	

1. Karnofsky Performance Status Scale			
10	**10**	Moribund; fatal processes progressing rapidly.	
11	**0**	Dead	

3. Charlson Comorbidity Index (CCI)

1. Age				Points
1	< 50 years		0	
2	50-59 years		+1	
3	60-69 years		+2	
4	70-79 years		+3	
5	> 80 years		+4	

2. Diabetes mellitus				Points
1	None		0	
2	Uncomplicated		+1	
3	End-organ damage		+2	

3. Liver disease				Points
1	None		0	
2	Mild		+1	
3	Moderate to severe		+3	

4. Solid tumor				Points
1	None		0	
2	Localized		+2	
3	Metastatic		+6	

5. AIDS				Points
1	No		0	
2	Yes		+6	

6. Moderate to severe Chronic Kidney Disease				Points
1	No		0	
2	Yes		+2	

7. Congestive Heart Failure				Points
1	No		0	
2	Yes		+1	

8. Myocardial infarction				Points
1	No		0	
2	Yes		+1	

9. Chronic Obstructive Pulmonary Disease				Points
1	No		0	
2	Yes		+1	

10. Peripheral vascular disease				Points
1	No		0	
2	Yes		+1	

11. Cerebrovascular Accident/Transient Ischemic Attack				Points
1	No		0	
2	Yes		+1	

12. Dementia				Points
1	No		0	
2	Yes		+1	

13. Hemiplegia				Points
1	No		0	

2	Yes		+2	

14. Connective tissue disease				Points
1	No		0	
2	Yes		+1	

15. Leukemia				Points
1	No		0	
2	Yes		+2	

16. Malignant lymphoma				Points
1	No		0	
2	Yes		+2	

17. Peptic ulcer disease				Points
1	No		0	
2	Yes		+1	

18. **TOTAL SCORE**	

4. Infection's classification

1. Place of acquisition		
Community-acquired: infections that were present at hospital admission or within 48 hours of admission that did not met criteria for healthcare-associated infection.	1	
Healthcare-associated: infections that were present at hospital admission or within 48 hours of admission that met one of the following criteria: - intravenous therapy took at home, wound treatment or specialized nursing care through an healthcare agency, family or friends; - had self-delivered intravenous medical therapy within 30 days previous to the infection; - attended an hospital or haemodialysis clinic or intravenous chemotherapy received 30 days before; - had an hospitalization in an acute care hospital for at least 2 days in the past 90 days; - inhabited in a nursing home or long-term care facility.	2	

1. Place of acquisition		
Hospital-acquired: infections that were not present or incubating at the time of hospital admission but that become evident after the first 48 hours.	3	

2. Extent of Infection		
Uncomplicated IAI: an infection that only involves a single organ and does not extend to the peritoneum.	1	
Complicated IAI: an infection that extends beyond a single organ into the peritoneal space, causing peritoneal inflammation.	2	

3. Localization of infection

Appendix	1	
Biliary Tract	2	
Colon	3	
Small Intestine	4	
Stomach/Duodenum	5	
Other:_____	6	

4. Post-operative Infection

Perforation	1	
Suture Dehiscence	2	
Tertiary Peritonitis	3	
Undetermined	4	
Other:_____	5	
Non Applicable	9999	

5. Microorganisms

Aerobes		
Gram-negative bacilli		
Enterobacter spp.	1	
Escherichia coli	2	

Aerobes		
Gram-negative bacilli		
Klebsiella spp.	3	
Proteus mirabilis	4	
Pseudomonas aeroginosa	5	
Salmonella spp.	6	
Other:_____	7	
Non Applicable	9999	

Gram-positive cocci		
Coagulase-negative *Staphylococcus*	8	
Enterococcus faecalis	9	
Enterococcus faecium	10	
Enterococcus (other)	11	
Staphylococcus aureus	12	
Streptococcus spp.	13	
Other:_____	14	
Non Applicable	9999	

Anaerobes		
Peptostreptococcus spp.	15	
Bacteroides spp.	16	
Clostridium spp.	17	
Other:_____	18	
Non Applicable	9999	

19. **Where** was the **pathogen isolated**? _____

20. **Were** blood cultures **taken**?	1		Yes	2		No
21. **Positive** blood cultures?	1		Yes	2		No

6. Resistance of isolated pathogens

Pathogen	Penicilina G	Ampicilina	Met/Oxacilina	Piperacilina/Tazob	Amox/Ac Clav	Cefalosporinas 1ªG	Cefoxitina	Cefuroxime	Ceftazidima	Cefotaxima	Cefepime	Tigecicilina	Imip/Meropnem	Ertapenem	Aztreonam	Eritromicina	Azitromicina	Clindamicina	Metronidazol	Vancomicina	Teicoplanina	Amicacina	Gentamicina	Tobramicina	Estreptomicina AC	Ciprofloxacina	Levofloxacina	Cotrimoxazol	Tetracicina	Linezolide	Rifampicina	Colistin
1.																																
2.																																
3.																																
4.																																

Legend - **Microorganisms**	
1	
2	
3	
4	

7. Treatment

1. Empirical therapy administered to the patient in the first 24 hours after diagnosis		
Antibiotic	Daily dose (total amount given in the first 24 hours)	Route of administration

2. Was the **initial** antibiotic therapy **changed**?	1 ☐ Yes	2 ☐ No

2.1. If **it was**, please **specify** the reason for change:	
Clinical deterioration	1 ☐
Directed towards sensitivity profile of isolated pathogen	2 ☐

2.1. If **it was**, please **specify** the reason for change:		
No evidence of infection	3	☐
Side effects	4	☐
Other: _____	5	☐
Non Applicable	9999	☐

3. Was the initial empiric antibiotic therapy "**adequate**"?	1	☐	Yes	2	☐	No

If the initial antibiotic prescribed within 24 hours matched in vitro susceptibility of a pathogen deemed to be likely cause of infection and when the dosage and route of administration are appropriate for current medical status (focus and severity of infection); only patients with positive microbiology are considered in this analysis

8. Risk factors for healthcare-associated infection

1. Previous colonization/infection by DR pathogen	1	☐	Yes	2	☐	No	3	☐	Unknown
2. Previous antibiotic therapy (last 3 months)	1	☐	Yes	2	☐	No	3	☐	Unknown
3. Previous hospital admission (last year)	1	☐	Yes	2	☐	No	3	☐	Unknown
4. Previous invasive procedures (last year)	1	☐	Yes	2	☐	No	3	☐	Unknown
5. Residence in a long-term care facility or nursing home	1	☐	Yes	2	☐	No	3	☐	Unknown

9. Outcome

1. At hospital discharge	1	☐	Dead	2	☐	Alive

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